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## THE EFFECT OF SUCCESSIVE REMOVAL UPON THE RATE OF REGENERATION

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One of the most interesting facts in connection with regeneration is the ability to replace a part after repeated removal. Former studies by the writer show that as a rule the rate of regeneration following a removal is no greater than that following second and later removals if the effect of age is eliminated. Where a difference exists it is in favor of the later regeneration.

The matter is of very great interest in connection with general problems of development and particularly in connection with the question as to the existence or non-existence of a necessary limit to the amount of living substance that a single individual may produce during its life cycle. Does the production of a group of tissues use up a part of a certain store of developmental energy possessed by the individual or is this store inexhaustible or perchance even increased by exercise of the function? These questions warrant more extended study especially in view of the additional analysis that has been made of other factors controlling the rate of regeneration. The new data support the conclusion previously reached and make possible a further analysis of the character of the difference between successive regenerations.

In making a comparison of successive regenerations a method must be devised for eliminating the effect of age. If the rate of a second regeneration is compared with that of a first regeneration in the same individual any difference that is made out may be due not to the pure effect of successive injury but to the effect of difference in age.

The method pursued in the present experiments consists in the initial removal of a portion of the tail in one-half of a set of Amphibian larvae of equal age. When regeneration has proceeded for several days there is a second removal of the part accompanied by a first removal in the half of the set that had not previously been operated upon. The second regeneration that ensues in one-half of the set may be compared directly with the first regeneration in the other half. There is no difference in age.

In experiment I approximately one-half of the tail was removed in tadpoles of the green frog, *Rana clamitans*. At six days the average first regeneration length is 2.01 mm. and the average second regeneration length 2.18 mm. The first exceeds the second in five sets and the

second exceeds the first in six. The corresponding specific lengths or lengths regenerated per unit of removed length are 0.194 and 0.205. The first regeneration exceeds the second in two sets, the second exceeds the first in five and one is tied. The second regeneration has the advantage in all the comparisons.

At eight days the average first regeneration length is 3.06 mm. and the second 3.42 mm. The first exceeds the second in three sets and the second exceeds the first in seven. The corresponding average specific lengths are 0.298 and 0.323. The first regeneration exceeds the second in four sets and the second exceeds the first in six. The second regeneration has the advantage in all the comparisons.

This advantage of the second regeneration over the first in experiment I holds true of second regenerations from both old and new tissue levels.

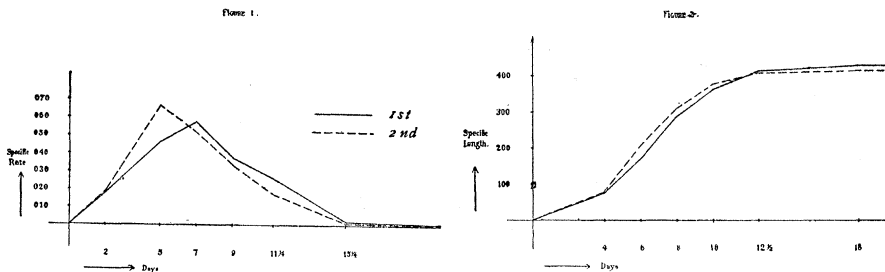


FIG. 1. CHANGE IN SPECIFIC RATE OF REGENERATION DURING THE REGENERATION PERIOD FOR BOTH FIRST AND SECOND REGENERATIONS. TADPOLE TAIL OF RANA CLAMITANS. UNBROKEN LINE = FIRST REGENERATION. BROKEN LINE = SECOND REGENERATION.

FIG. 2. SPECIFIC REGENERATED LENGTHS DURING THE REGENERATION PERIOD FOR BOTH FIRST AND SECOND REGENERATIONS. TADPOLE TAIL OF RANA CLAMITANS. UNBROKEN LINE = FIRST REGENERATION. BROKEN LINE = SECOND REGENERATION.

In experiment II, also with *Rana clamitans*, operations were made at the  $\frac{1}{10}$ ,  $\frac{1}{3}$ ,  $\frac{1}{2}$  and  $\frac{2}{3}$  levels in a sufficient number of individuals to yield valid data. Regeneration measurements were made at each of these levels 4, 6, 8, 10,  $12\frac{1}{2}$ , 18 and 56 days after the operations. The second regeneration at these levels is ahead of the first until about the twelfth day after which the first regeneration catches up. The maximum rate for both regenerations is reached before this time, and earlier for the second than for the first regeneration. The relation between the rates is given in figure 1 and between the total regenerated lengths in figure 2.

In experiment III two-thirds of the tail was removed in larvae of the salamander, *Amblystoma punctatum*. A comparison of the first, second and third regenerations was made at 2, 4, 6, 8, 10 and 14 days. At two days the first, second and third regenerations average respec-

tively 0.22, 0.25 and 0.26 mm. The corresponding values at four days are 0.66, 0.75 and 1.00; at six days 1.36, 1.40 and 1.36; at eight days 2.18, 2.68 and 2.68; at ten days 3.55, 3.82 and 4.20; at fourteen days 5.34, 6.12 and 6.08. The advantage is in favor of the second and third regenerations as opposed to the first and of the third as opposed to the second. Individual comparisons at each of the different times show similar results.

The evidence as a whole shows clearly that when the age factor is eliminated there is no decrease in rate of regeneration with successive removal. On the contrary the second regeneration is more rapid than the first up to the period of maximum rate. The second regeneration however passes its maximum sooner than does the first and after the tenth day the latter therefore catches up in total amount regenerated. There is no striking difference between the second and the third regenerations but in each comparison the third has a slight advantage.

When successive regenerations within single individuals are compared there is a progressive decrease in rate and it is obvious that this is due to age.

The possibility has suggested itself that the second regeneration starts out at a more rapid rate than the first because the cells at the cut surface were undergoing regenerative changes at the time of the new operation and can therefore start the process much faster than can the old cells at the first surface of regeneration. Following a first removal there is a considerable degree of reorganization of the cells at the cut surface, accompanied by active migration. During this period which in *Rana clamitans* lasts two or three days there is little or no mitotic cell division. Then follows a division period which reaches its maximum at seven to ten days. Its decline is associated with the oncoming of tissue differentiation.

A special study has been made of the relative rates of second regeneration from old cells following a cut inside of the first removal level and from new cells following a cut outside of the first level. This comparison shows only a very slight difference in favor of the new cells and this is largely confined to the early stages, the period of cell migration.

The period of increase in rate is the period of active cell multiplication and the decline in rate is associated with cell differentiation. The second regeneration therefore reaches the period of differentiation slightly in advance of the first regeneration.

Apart from the slowing due to age there is no indication of a limitation of the amount of new material that may be produced by regeneration. The actual limitation comes not from the using up of regenera-

tive or developmental energy or of 'determiners' by repeated regeneration but from changes in the non-regenerating part associated with age. In another place there is a discussion of the possibility that there may be an effect upon the rate of developmental processes in the organism as a whole due to continued regeneration of a part. This is studied particularly in connection with the effect of regeneration upon rate of metamorphosis in *Amphibia*.

Regeneration studies in general and those on successive regeneration in particular make it improbable that there is a definite number of cell regenerations between the fertilized egg and the end product, the differentiated cell. The possibility that certain cells may remain in an early cell generation can not be wholly excluded as an explanation of at least part of first regeneration phenomena. Under suitable stimulation such cells may be postulated to take up development where it has left off. The definite descriptions of de-differentiations of cells as well as other facts of regeneration argue against this conclusion. The view that there can be no such definite number of cell generations is strengthened by the facts of successive regeneration. It does not seem probable that embryonic cells of an early cell generation can be held in reserve through repeated regenerations.

The explanation of regeneration by the theory of duplicate sets of determiners meets difficulties in undiminished successive regenerations. The greater the number of repeated regenerations the greater the difficulties of explanation on this basis. Of course the difficulty does not hold for the hypothesis that every cell or nearly every cell contains a full set of determiners.

The earlier appearance of the maximum rate in the second than in the first regeneration may be due to the more rapid progress of the cells in the early cell migration period alone or it may be due to the acceleration of the whole developmental cycle.

The full data will be published in the *University of Illinois Biological Monographs*.

## THE GEOLOGIC RÔLE OF PHOSPHORUS

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Phosphorus appears in nature in many forms and in many situations. Its numerous transformations, however, follow an orderly sequence. In a broad way, the changes form a cycle but since the path of change